REVIEW

Prospects for atherosclerosis regression through increase in high-density lipoprotein and other emerging therapeutic targets

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In a process often seen as progressive and irreversible, deposition and retention of lipoproteins and the consequent inflammatory reaction result in the accumulation of atherosclerotic plaques from an early age. However, striking effects observed in experimental models support the concept that atherosclerosis can regress. This is often accompanied by changes in plaque composition favouring stability and decreased likelihood of rupture. Large clinical trials have established the value of low-density lipoprotein cholesterol reduction with statin treatment, although this may prevent no more than 30% of all cardiovascular events, and the magnitude of effect on plaque regression seems relatively modest. High-density lipoprotein cholesterol (HDL-C) is well recognised as an important and independent protective factor, although treatment options to increase HDL-C have until now been limited. The recent emergence of new treatments will probably establish increased HDL-C as another important strategy in antiatherosclerosis treatment. Beyond HDL-C increases, further appreciation of mechanisms of cellular lipid homoeostasis and regulation of gene transcription have revealed new targets for atherosclerosis treatment. This review considers emerging approaches to plaque regression together with some of the parallel developments in imaging technology that will improve our appreciation of response to treatment.

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Atherosclerosis is initiated by the deposition, retention and oxidative modification of apolipoprotein (apo)B-containing lipoproteins, notably low-density lipoprotein cholesterol (LDL-C) in the vessel wall. This is associated with endothelial dysfunction and recruitment of monocytes that take up oxidised LDL to become macrophage-derived foam cells, collectively apparent macroscopically as ''fatty streaks''. Subsequent proliferation of vascular smooth muscle cells and secretion of extracellular matrix contribute fibrous elements, whereas accumulation of lipid and inflammatory cell debris forms the necrotic lipid core of the mature atherosclerotic plaque. Both the size and composition of plaques determine the clinical course. The so-called ''vulnerable plaque'' typically has a large lipid core, thin fibrous cap and inflammatory cell infiltrate. Acute atherothrombotic complications arise when rupture or erosion of the cap exposes thrombogenic plaque components.

Animal models have contributed considerably to our understanding of atherogenesis and the influence of lipids and lipid-modifying treatments. In early work, feeding a high-fat diet to monkeys caused hypercholesterolaemia and accelerated the development of atherosclerosis. Subsequent resumption of a normal diet induced moderate disease regression.[4] More recently, mouse models that permit precise genetic manipulation have come to predominate. Normal mice have total plasma cholesterol of about 2.5 mmol/l (100 mg/dl), of which the majority is high-density lipoprotein cholesterol (HDL-C), and are resistant to atherosclerosis. However, mice lacking apoE, which is involved in the clearance of circulating lipoproteins, are markedly hypercholesterolaemic and develop atherosclerotic lesions that become complex and share some features in common with those found in humans. Correction of hypercholesterolaemia and subsequent regression of early foam cell lesions has been attained by somatic apoE gene transfer using an adenovirus vector.[5] However, short-lived expression of apoE is a limitation that precludes the study of regression of advanced, more clinically relevant, lesions. Instead, such lesions have been studied by the transplantation of an atherosclerotic aortic segment from apoE-deficient mice into syngeneic wild-type mice with a non-atherogenic lipid profile.[6] In this model, reducing cholesterol by 90% produced substantial reductions in the size and foam cell content of atherosclerotic lesions (fig 1).

The first experimental evidence of a protective effect of HDL-C elevation was obtained by Badimon *et al*.[7] Serial injections of purified HDL into cholesterol-fed rabbits resulted in diminished atherosclerosis after 90 days, relative to controls. More recently, the ability to attain sustained HDL-C increases in mice by transgenic expression of its principal apolipoprotein, apoA-I, has enabled a series of experiments determining the effects of HDL-C increases on plaque size and composition,[8 9] in addition to effects on remodelling advanced (American Heart Association classes III–V) plaques.[10]

Abbreviations: ACAT, acyl-coenzyme A:cholesterol acyltransferase; apo, apolipoprotein; ApoAIMilano, a mutant form of apoAI; BIP, bezafibrate infarction prevention; CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor

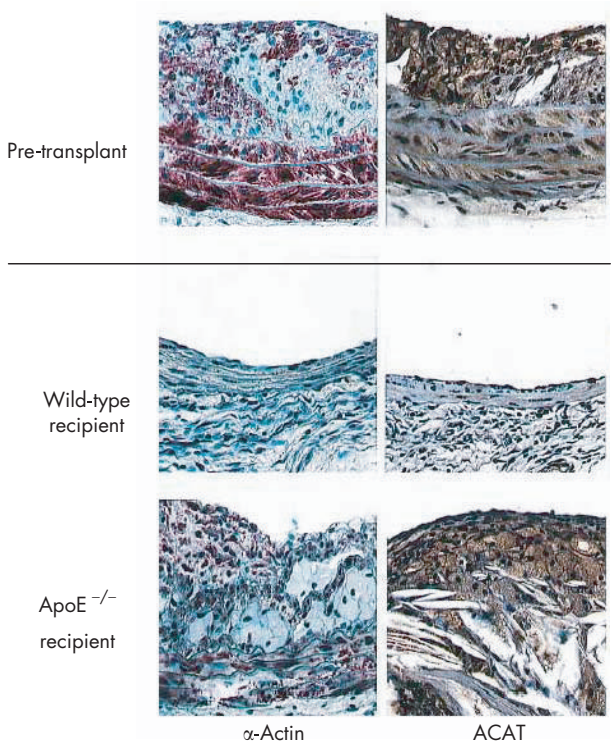

Figure 1 Experimental atherosclerosis regression in mice. The top row shows the extent of atherosclerosis that had been allowed to develop in an apolipoprotein E-deficient (apoE$^{-/-}$) mouse before transplantation into the low-density lipoprotein, high-density lipoprotein metabolic environment of a wild-type mouse (middle row) or hypercholesterolaemic apoE$^{-/-}$ control (bottom row). Note the profound lesion regression in the wild-type mouse, where foam cell staining is absent. Contrast the progression of atherosclerosis in the control. Panels on the left have been immunostained for the smooth muscle cell marker α-actin and in the right-sided panels for acyl-coenzyme A:cholesterol acyltransferase (ACAT), which is present in macrophage-derived foam cells. Adapted from Reis *et al*.[6]

The dynamic, reversible nature of atherosclerosis shown in these animal experiments raises the exciting possibility that, by using potent new treatments, clinically important plaque regression and remodelling may be attainable in humans. However, enthusiasm for these findings should be tempered with the caveat that discoveries in animal models do not always lead to effective clinical treatments—see later discussion of acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitors.

LDL-C LOWERING IN CONTEXT

In humans, LDL-C can be lowered effectively, and successive guidelines have advocated progressively lower LDL-C targets: currently, 70 mg/dl (1.8 mmol/l) has been suggested for secondary prevention in the patients with highest risk.[11] However, even with optimal LDL-C lowering, there remains a relatively high risk of atherothrombotic events. For example, the treatment group in the Heart Protection Study retained a 5-year risk of 19.8% of sustaining a major vascular event (vs 25.2% in the placebo group).[1] Further substantial risk reduction is likely to require alternative approaches, such as HDL-C increases and direct targeting of pathological processes in the atherosclerotic plaque itself (fig 2).

From epidemiological observations, HDL-C is a stronger predictor of risk than LDL-C.[3] Each percentage increase in LDL-C increases risk by approximately the same; however, each percentage decrease in HDL-C is accompanied by a 2–3% increase in risk.[12] Increased cardiovascular risk associated with low HDL-C persists at all levels of LDL-C and there also seems to be synergy such that the effects of HDL-C are much more pronounced where non-HDL-C is low. This suggests that a clinical strategy of simultaneously lowering LDL-C to reduce cholesterol deposition in the vessel wall, and raising HDL-C to promote reverse cholesterol transport, might produce considerable plaque regression.

Potentially beneficial effects of HDL increase include reverse cholesterol transport HDL-C and anti-inflammatory and anti-oxidant actions in vitro.[13 14] One mechanism of benefit from HDL increase could be improvement in endothelial function observed after infusion of reconstituted HDL-C.[15]

CURRENT APPROACHES FOR HDL-C INCREASE

To date, relatively few studies have examined HDL-C increase—largely owing to a lack of efficacious drugs. Currently available lipid-modifying agents that can raise HDL-C include statins, fibrates and nicotinic acid. Table 1 summarises the current and emerging lipid treatments and their effect on HDL-C.

The Veterans' Administration HDL Intervention Trial compared gemfibrozil 1200 mg/day with placebo in men with coronary disease and HDL-C $\leqslant$1 mmol/l. After 5 years' median follow-up, there was a 24% reduction in a composite myocardial infarction/death/stroke endpoint.[16] HDL-C was higher in the treatment group by a modest 6%, whereas LDL-C was no different, again suggesting that there may be additional benefit from combined treatment with a statin. The Bezafibrate Infarction Prevention (BIP) study found only a trend to risk reduction with bezafibrate 400 mg/day versus placebo.[17] However, the BIP study patients had higher HDL-C at entry, and comprised a smaller proportion of patients with diabetes and metabolic syndrome who are known to be at high risk and who may benefit disproportionately from HDL-C increase. Indeed in a post hoc analysis of the subgroup of patients with high triglycerides in the BIP study, there was a 39.9% reduction in myocardial infarction/sudden death. Similarly, subgroup analysis of the results of the Veterans' Administration HDL Intervention Trial showed that the patients with diabetes as well as those without diabetes with insulin resistance actually received most benefit.[18] In the recent Fenofibrate Intervention and Event Lowering in Diabetes study, patients with type II diabetes and total cholesterol:HDL-C ratio >4 (or triglycerides >1 mmol/l) were treated with fenofibrate to a minimum 5-year follow-up.[19] HDL was increased over placebo by a modest 5% at 1 year, falling to around 1% by the end of the study. This only resulted in non-significant improvement in the primary endpoint of combined events and an 11% decrease in total cardiovascular events, driven by decreases in myocardial infarction and need for revascularisation. Interpretation and applications are hindered by the exclusion of statins at study outset and by subsequently higher statin usage in the placebo group (17% placebo and 8% fenofibrate).

Nicotinic acid is the most efficacious HDL-C increasing agent available for clinical use. Studies with the early immediate release formulation were limited by side effects, notably flushing, but a modified release formulation seems much better tolerated.[20] The Coronary Drug Project of the 1970s showed a reduction in major adverse cardiac events after 6 years' nicotinic acid treatment and late (15-year) follow-up was associated with an 11% late reduction in mortality.[21] In this pre-statin era trial, the extent to which the effects were due to LDL-C reduction (also a benefit of nicotinic acid) or HDL-C increase is uncertain. The combination of statin and nicotinic acid was used in the HDL-Atherosclerosis Treatment Study—in the treatment group, progression of coronary stenoses assessed using quantitative angiography was attenuated.[22] However, interpretation of the results of this study is hindered by the lack

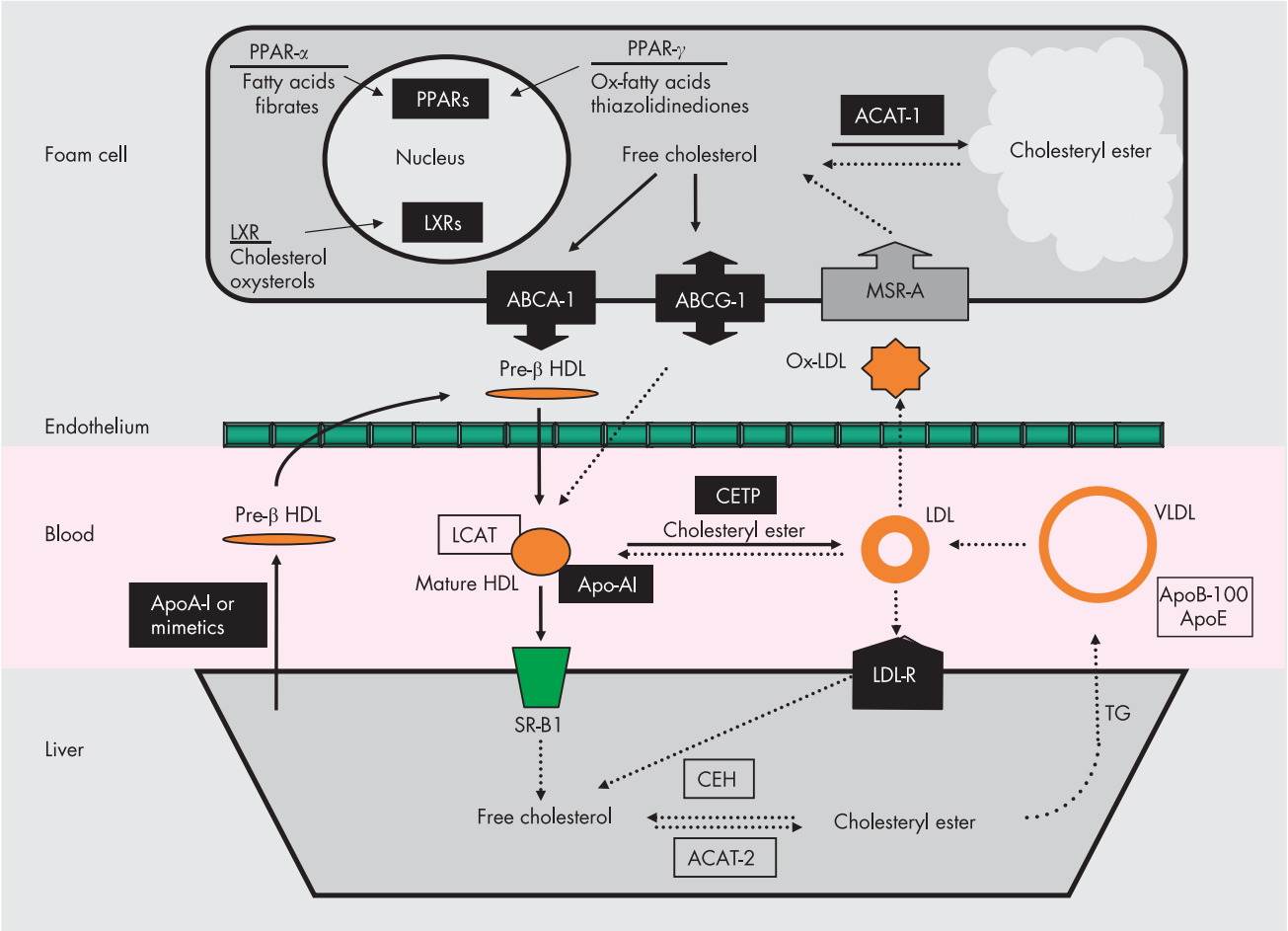

Figure 2 Schematic of cholesterol transport pathways and targets for therapeutic interventions. Excess free cholesterol is transferred from cells to nascent high-density lipoprotein (HDL) particles by the ATP-binding cassette (ABC) family of proteins. Free cholesterol is then esterified by the enzyme lecithin:cholesterol acyl transferase (LCAT) and sequestered in the core of the mature HDL particle. Cholesteryl ester transfer protein (CETP) exchanges cholesteryl ester from HDL with triglyceride from apolipoprotein (apo)B-containing lipoprotein particles. Alternatively, HDL-cholestrol can be directly taken up by the liver via the scavenger receptor type B1 (SR-B1). Targets for therapeutic intervention are shown as solid black symbols. ACAT, acyl-coenzyme A:cholesterol acyltransferase; CEH, cholesteryl ester hydrolase; LDL, low-density lipoprotein; LDL-R, LDL receptor; LXR, liver X receptors; MSR-A, macrophage scavenger receptor type A; ox-LDL, oxidised LDL; PPAR, peroxisome proliferator-activated receptor; TG, activated receptors. The molecules listed under the nuclear hormone receptors are some of their known ligands.

of a statin-only treatment arm for comparison. More recently, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol Study 2 reported that in patients whose LDL-C was already treated to target with statins (mean 2.2 mmol/l), addition of low-dose nicotinic acid 1 g/day seemed to retard the progression of atherosclerosis, measured by ultrasound assessment of carotid intima media thickness.[23] Larger clinical outcome studies with this drug are now under way (eg, Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglyceride and Impact on Global Health study, results expected 2011).

EMERGING HDL-C-RELATED STRATEGIES

Cholesteryl ester transfer protein (CETP) mediates exchange of hydrophobic lipids between HDL and apoB-containing lipoproteins (fig 2). The net effect is to deplete HDL of cholesteryl ester and to substitute triglycerides. Thus, inhibition of CETP favours carriage of cholesterol by HDL rather than by atherogenic lipoproteins. Several agents are at the clinical trial stage and recent data show a 60% increase in HDL-C after short term treatment with toracetrapib in combination with statin.[24] Although experimental evidence seems to support the concept of CETP inhibition as atheroprotective,[25] a degree of caution is warranted. Accumulation of cholesteryl ester in large HDL particles may increase the measured level of HDL-C but does not necessarily indicate increased functionality in respect of reverse cholesterol transport, although a recently presented study seems to confirm that HDL from CETP-treated individuals retains its capabilities as a cholesterol acceptor.[26] Transfer of cholesteryl ester to apoB-containing lipoproteins and subsequent hepatic disposal may itself be a route of reverse cholesterol transport. In this respect, it was recently reported that despite increases in HDL-C and apoA-I levels after treatment with a CETP inhibitor, faecal sterol excretion was not increased.[27] Furthermore, several mutant forms of CETP exist, however, not all of these appear beneficial as some confer increased cardiovascular risk despite raised HDL-C levels.[28] Recently the ILLUMINATE study of more than 15 000 subjects comparing atorvastatin versus atorvastatin and the CETP inhibitor torcetrapib was halted because of excess mortality in torcetrapib arm (51 vs 82). The causes of excess death are not yet publicly available. Torcetrapib has been withdrawn from patient use by its manufacturer.

Table 1 Current and emerging lipid treatments and their effect on high-density lipoprotein-cholestrol (HDL-C)

	Mode of action	HDL-C	Main adverse effects
Current agents			
Statins	HMG-CoA inhibition "pleiotropic effects"	↑ ~5%	Liver, myopathy
Fibrates	PPARα agonist	↑ ~10%	Liver, myopathy, gastrointestinal s/e
Nicotinic acid	↓ Adipocyte lipolysis direct effect on plaque?	↑ ~25%	Flushing, dyspepsia, liver, myopathy
Emerging agents			
ACAT inhibitors	ACAT inhibition	No effect	Unknown
Thiazolidinediones	PPARγ agonist	↑ ~5%	Oedema, ↑ heart failure
CETP inhibitors	↓ Cholesterol exchange between lipoproteins	↑ >60%?	Unknown
ApoA-I mimetics	↑ Reverse cholestrol transport? Anti-oxidant? Anti-inflammatory?	Unknown	Unknown

ACAT, acyl-coenzyme A:cholesterol acyltransferase; Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HMG-CoA, 3-hydroxy-3-methyl glutaryl coenzyme A; PPAR, peroxisome proliferator-activated receptor; s/e, sepsis and/or endocarditis.

Individuals possessing a mutant form of apoA-I (ApoAIMilano) have low HDL-C, but paradoxically are protected from atherosclerotic disease,[29] probably through enhanced reverse cholesterol transport.[30] In mice, administration of a single high dose of apoAIMilano protein brought about plaque regression and favourable lesion remodelling.[31] Quantifying human coronary atherosclerosis with intravascular ultrasound, Nissen *et al*[32] recently reported a 4% reduction in coronary plaque volume after only five weekly infusions of recombinant ApoAIMilano. Peptide mimetics of apoA-I such as D4F, which contain a cholesterol-binding domain and can be given orally, are being investigated and have been shown to be effective in retarding plaque progression in mouse models of atherosclerosis.[33]

TARGETING ATHEROGENESIS AT THE LEVEL OF THE PLAQUE

Modifications of LDL-C and HDL-C outlined above may have indirect effects on plaque biology, but there is also increasing interest in developing direct plaque interventions. Targets include inflammation and thrombogenicity, and pathways of cholesterol uptake and efflux from macrophages. Many genes involved in macrophage lipid homoeostasis and the inflammatory process are collectively under the control of certain transcriptional regulators (notably peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs)). These nuclear receptor families have both endogenous and exogenous ligands and control multiple aspects of glucose and lipid metabolism.[34] Fibrate and thiazolidinedione (glitazone) drugs are agonists of PPARα and PPARγ, respectively. One attractive strategy is to increase evacuation of foam cell cholesterol by upregulating expression of the ATP-binding cassette proteins—membrane transporters that mediate cholesterol transfer from cells to HDL that are under the transcriptional control of the LXR and PPAR families.

In a study of the PPARγ agonist rosiglitazone, in patients with coronary artery disease but without diabetes, the treatment group showed reduced progression of carotid atherosclerosis compared with controls.[35] The recently reported PROspective pioglitAzone clinical trial in macrovascular events study showed a 16% relative reduction in the secondary endpoint of all-cause mortality, non-fatal myocardial infarction and stroke in patients with type 2 diabetes and evidence of prior macrovascular disease.[36] More research is required before widespread adoption of the glitazones as antiatherosclerotic treatments—for instance, rosiglitazone and pioglitazone differ markedly in their effects on lipids, in particular on triglycerides and LDL-C.[37] Further PPAR agonists are under development, including combined agonists of PPARα and PPARγ. LXR agonists are also under development, but one problem might be lack of specificity. Current LXR agonists under investigation seem able to activate expression of ATP-binding cassette proteins, and have provided encouraging preliminary effects in mouse atherosclerosis.[38] However, direct translation to human use will require the development of more specific LXR agonists as currently available drugs have been associated with the development of hepatic steatosis.

The enzyme ACAT esterifies cholesterol for non-toxic intracellular storage. Enzymes with ACAT activity are present in multiple tissues including the liver and intestine. In the context of atherosclerosis, the ACAT-1 subtype present in macrophages catalyses the production of cholesteryl ester, which accounts for foam-cell formation. Compounds with ACAT-inhibitory properties reduce cholesterol loading in cell culture and atherosclerosis in mice.[39] However, in humans, addition of the ACAT inhibitor avasimibe to standard treatment, including statins, in patients with coronary atherosclerosis had no beneficial effect on plaque size assessed by intravascular ultrasound.[40] Indeed, avasimibe treatment was associated with increased plasma LDL-C, possibly owing to induction of cytochrome P450 3A4 activity and consequent inactivation of statins.

IMAGING ATHEROSCLEROTIC PLAQUES

One of the challenges to studies of plaque regression in humans is to identify, and preferably quantify, changes in response to treatment. If the exciting prospects of clinically important regression and favourable remodelling of atherosclerosis are to be realised, it will be vital to develop diagnostic tools that image plaques directly as opposed to indirectly by their encroachment on the vessel lumen. The arterial wall can remodel to accommodate considerable plaque burden without affecting the lumen until atherosclerosis is relatively advanced.[41] Consequently, imaging the vessel wall itself is likely to be more sensitive to changes. Quantitative coronary angiography studies of lipid lowering, despite the known clinical benefit, show only small changes in angiographic appearance of coronary stenoses. Techniques with greater sophistication will also allow plaque composition, potentially even at the molecular and cellular levels, to be determined.

Assessment of arterial wall intima-media thickness by ultrasound most commonly in the carotid has been shown to correlate with the atherosclerosis burden elsewhere and also to

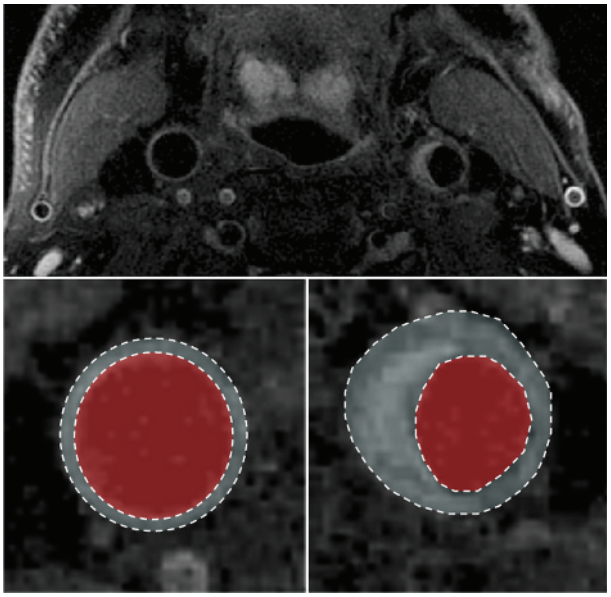

Figure 3 High-resolution T2-weighted transverse MRI of the neck. The upper panel shows a normal smooth-walled right carotid artery. By contrast, the left carotid contains a large heterogeneous eccentric atherosclerotic plaque. The lower panel shows the method for quantifying vessel wall area (shaded). Serial quantification of anatomically aligned slices can be used for studies of atherosclerosis progression and regression in humans.

predict the risk of future cardiovascular events. This has been used in a number of trials to show that statin treatment can cause moderate regression of disease.[42] Similarly, intravascular ultrasound has been used to show serial changes in plaque burden in the coronary arteries[43] and can to some extent also examine plaque morphology. This is a powerful technique that has been widely adopted, but has the obvious drawback of being invasive. Further discussion is beyond the scope of this review, but interested readers are directed elsewhere for further information.[44]

MRI at 1.5–3 T field strength offers reproducible, high-resolution, non-invasive in vivo plaque quantification and characterisation (fig 3), and does not involve ionising radiation. Using MRI, Corti *et al*[2] detected considerable regression of plaques in the aorta and carotid arteries of patients treated with simvastatin for 12 months. The sensitivity of the technique allowed these findings to be observed in as few as 18 patients. Using the same approach, this group has also investigated the effects of prolonged statin treatment[45] and high-dose versus low-dose treatment.[46] MRI also has the capability to characterise plaque composition on the basis of appearance on different image weightings such as T1 or T2, and this has been used to show reduction in carotid plaque lipid content after intensive lipid-lowering treatment.[47] MRI of coronary atherosclerosis is clearly desirable. There have been preliminary reports showing feasibility of coronary artery wall MRI,[48] but further progress remains challenging owing to the anatomically deep location, small size and unpredictable course of the coronaries, although cardiac and respiratory motion present further obstacles. Magnetic resonance contrast agents are also under development, which will provide targeted imaging of specific molecules, cell types and processes to fully characterise atherosclerosis and its complications.

CONCLUSIONS

Studies in animals have shown strong potential for atherosclerosis regression in the presence of a favourable metabolic environment. In isolation, LDL-C reduction with statins prevents only a minority of vascular events. Emerging strategies for additional atherosclerosis treatment include increasing HDL-C to promote reverse cholesterol transport and direct targeting of plaque inflammation and macrophage lipid metabolism. Recent studies using vascular MRI in vivo to characterise the arterial wall in humans have already shown that a modest degree of regression is possible in humans with aggressive statin treatment alone. The timely convergence of advanced imaging techniques and new approaches to treatment make clinically important plaque regression in humans an appealing and realistic prospect.

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